# Comparison of Insulin Analogs and Human Insulins: A Narrative Review

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## Abstract

**Introduction** Since insulin analogs have pharmacological properties that are similar to the normal physiological action of insulin, it has been suggested that they provide better glucose control and less rates of hypoglycemia compared to human insulins.

**Methods** We performed a narrative, nonsystematic review of the literature including clinical trials, systematic reviews, meta-analyses, and professional guidelines related to the comparison of human insulins and insulin analogs in terms of glucose control, safety profile, and cost.

**Results** Long-acting basal insulins result in mild improvement in glucose control and less rates of nocturnal hypoglycemic compared to neutral protamine Hagedorn insulin, mainly among patients with type 1 diabetes. Rapid-acting insulin analogs provide better glucose control and lower rates of hypoglycemia compared to regular insulin among patients with type 1 diabetes, whereas no advantage has been shown for insulin analogs among patients with type 2 diabetes for glucose control or hypoglycemia. Premixed insulin analogs provided no advantage in glucose control and inconsistent benefit in lowering the rates of hypoglycemia compared to human premixed insulins among patients with type 2 diabetes. The cost of insulin analogs is significantly higher than human insulins, and favorable cost-effectiveness has only been demonstrated for rapid-acting insulin analogs in type 1 diabetes.

**Conclusion** Currently available evidence supports the use of rapid-acting insulin analogs and possibly long-acting basal insulin over human insulins for patients with type 1 diabetes. For patients with type 2 diabetes, the use of long-acting insulin analogs may be recommended for selected patients who are at an increased risk of significant hypoglycemia, while no clear benefits of meal insulin analogs over human insulins have been observed.

**Keywords**
► diabetes mellitus
► insulin analogs
► human insulins

## Introduction

The discovery of insulin is regarded as one of the greatest breakthroughs in the history of medicine. Before the availability of insulin, type 1 diabetes was considered a cause for limited life expectancy as patients would develop diabetic ketoacidosis and its fatal complications.[1] The earlier insulin preparations were obtained from animal sources, and it was not until 1982 when human insulin was produced by genetic engineering using recombinant DNA technology. Insulin analogs were developed by altering the chemical structure of insulin, resulting in new insulins that had actions closer to the normal physiological proprieties of insulin. The first insulin analog that became available was the rapid-acting insulin, lispro in 1996, while the first long-acting basal insulin analog, glargine became available in 2000. Other insulins analogs followed such as rapid-acting insulins, aspart and glulisine as well as basal insulins, detemir and degludec along with several forms of premixed insulin analogs such as aspart 70/30, lispro 75/25, lispro 50/50, and degludec/aspart 70/30.

The introduction of insulin analogs was accompanied by great enthusiasm, given their closer pharmacokinetic properties to normal insulin. The administration of rapid-acting insulin analogs results in a rapid increase followed by a quicker fall in insulin levels compared to regular insulin. This resulted in lower postprandial glucose levels which was suggested to translate into better overall glucose control and lower rates of hypoglycemia compared to human insulins.[2] On the other side, the action profile of basal insulin analogs had shown a longer duration of action and less variability compared to human insulins.[3] This newer class of insulin has been heavily promoted as providing more flexible schedules and a reduced risk of hypoglycemia compared to conventional human insulins. Insulin forms a significant part of the health budget of persons with diabetes. The increasing cost of insulin has steadily become a challenge, not only in low-income and middle-income countries but also in resource-rich settings.[4] The cost of insulin analogs is significantly higher than that of human insulins; therefore, the use of insulin analogs should be justified by the demonstration of better glucose control, more favorable safety profile, or cost-effectiveness.

We aimed to perform a narrative review to compare human insulins and insulin analogs, with a particular focus on the efficacy of lowering blood glucose, safety (in terms of rates of hypoglycemia and other side effects), quality of life, and cost consideration, including cost-effective analysis.

## Methods

We performed a literature review using MEDLINE, EMBASE, SCOPUS, Cochrane Central Register of Controlled Trails, and Cochrane Database of Systematic Reviews (from inception until 31 January 2023). Articles related to the comparison of insulin analogs and human insulins in patients with type 1 diabetes and those with type 2 diabetes were searched. The literature search included original articles, systematic reviews, meta-analysis, professional guidelines, and consensus statements published in English. We included articles that assessed aspects of comparison between insulin analogs and human insulins, including glucose control (as assessed by HbA1c levels, fasting blood glucose, and postprandial glucose levels), rates of hypoglycemia (included general, symptomatic, nocturnal, and severe forms), weight gain, rates of cardiovascular disease, quality of life, and cost analysis. We present a summary of the data separately depending on the type of diabetes (type 1 and type 2) along with sections on cost analysis and guidelines from professional organizations on the use of insulin analogs and human insulins.

### Type 1 Diabetes

Most clinical studies have shown no difference in glucose control between basal insulin analogs (glargine and detemir) and neutral protamine Hagedorn (NPH) insulin, while some studies have demonstrated a reduction in rates of hypoglycemia with long-acting basal analogs compared to NPH insulin.[5–22] There are no published clinical studies comparing insulin degludec to NPH insulin in patients with type 1 diabetes. The most recent Cochrane review on the use of basal insulin analogs compared to NPH insulin in patients with type 1 diabetes included 26 randomized controlled trials with 8,784 patients and had shown the following findings: insulin detemir lowered the risk of severe hypoglycemia compared to NPH insulin but this finding was not consistent; there was no difference in the incidence of severe hypoglycemia when comparing insulin glargine to NPH insulin; there was no difference in the occurrence of severe nocturnal hypoglycemia, glucose control, or quality of life when comparing insulin detemir or insulin glargine to NPH insulin; there were no differences in all those outcomes between children and adults.[23] In another systematic review that included 65 randomized and nonrandomized trials with 14,200 patients and was sponsored by the Canadian Health and Canadian Agency for Drugs and Technologies in Health, the authors found benefits of using long-acting basal insulin analogs compared to NPH insulin in patients with type 1 diabetes in terms of reduction of HbA1c, fasting plasma glucose, weight gain, and the incidence of major, serious, or nocturnal hypoglycemia.[24] A more recent systematic review included 28 randomized controlled trials with 7,394 patients and had shown statistically significant improvement of glucose control with the long-acting basal insulins analog glargine but not insulin detemir compared to NPH insulin (mean reduction of HbA1c of 0.31% with insulin glargine and mean reduction of 0.25% with insulin detemir compared to NPH insulin) and lower risk of severe hypoglycemia with basal insulin analogs.[25] One advantage that was shown with insulin detemir is less weight gain (average 0.6 to 1.6 kilograms) compared to NPH insulin.[7,8]

The benefits of rapid-acting insulin analogs over regular insulin in patients with type 1 diabetes were more obvious as most clinical studies found that the use of rapid-acting insulin analogs has resulted in mild improvements in HbA1c levels, reduction in rates of hypoglycemia and

decreased postprandial glucose levels compared to regular insulin.[25–42] The most recent Cochrane review on the use of rapid-acting insulin analogs compared to regular insulin in patients with type 1 diabetes included nine randomized controlled trials with 2,693 patients and had shown a slight improvement in HbA1c levels with insulin analogs (reduction by 0.15%) and no clear difference in rates of hypoglycemia.[43] A more recent systematic review that included 6,235 patients with type 1 diabetes found that rapid-acting insulin analogs were associated with lower HbA1c levels (reduction by 0.13%), lower postprandial glucose levels, and lower risk of total hypoglycemia episodes, nocturnal hypoglycemia, and severe hypoglycemia compared to regular insulin.[44]

## Type 2 Diabetes

Some clinical studies have shown that long-acting basal insulin analogs (glargine and detemir) were associated with a reduction in rates of hypoglycemia—mainly nocturnal type—in patients with type 2 diabetes, with no difference in glucose control, when compared to NPH insulin.[45–61] There are no published clinical studies that compared insulin degludec to NPH insulin in patients with type 2 diabetes. The latest published Cochrane systematic review on the use of long-acting insulin analogs compared to NPH insulin in patients with type 2 diabetes included 24 randomized controlled trials with 3,419 patients and had shown no difference in glucose control as indicated by HbA1c levels and lower rates of hypoglycemia including severe and nocturnal types with insulin glargine and detemir compared to NPH insulin.[62] A large observational study examined 25,489 patients with type 2 diabetes and found no difference in glucose control or rates of hypoglycemia leading to emergency department visits or hospital admissions when comparing long-acting basal insulin analogs to NPH insulin.[63]

For meal insulins, most studies in patients with type 2 diabetes have shown no difference in rates of hypoglycemia or glucose control but some studies have found a reduction in postprandial glucose levels with rapid-acting insulin analogs when compared to regular insulin.[29,64–66] The latest published Cochrane review on the use of rapid-acting insulin analogs compared to regular insulin in patients with type 2 diabetes included 10 randomized controlled trials with 2,751 patients and had shown no difference in glucose control or rates of hypoglycemia.[67] Similarly, the latest published meta-analysis showed no difference in glucose control between rapid-acting insulin analogs and regular insulin in patients with type 2 diabetes.[68]

One advantage of rapid-acting insulin analogs over regular insulin is that their quicker onset of action allows their use at the start of meals or after consuming the meals, compared with regular insulin which should be injected 30 minutes before meals. This feature is important in persons for whom the expected amount of consumed food cannot be anticipated, such as children. In such conditions, rapid-acting insulin is injected immediately after meals and the dose is calculated according to the amount of consumed carbohydrates.[69] Some clinicians use the same principle in elderly people when the quantity of consumed food cannot

be predicted, and therefore, rapid-acting insulin may be preferred for easier dose adjustments according to the carbohydrate content of meals. Even though this idea appears attractive, supportive evidence for such practice is limited.[70]

Premixed insulins are used only in some patients with type 2 diabetes, while it is recommended to use a regimen of basal and meal insulin for patients with type 1 diabetes.[71]

Clinical studies have shown that premixed insulin analogs are similar to premixed human insulins in reducing fasting glucose levels and HbA1c levels, with some studies showing a reduction in postprandial glucose levels with premixed insulin analogs. There was no difference in rates of hypoglycemia between premixed insulin analogs and premixed human insulins.[72–77] The Agency for Healthcare Research and Quality in the United States examined the comparative effectiveness of premixed insulin analogs compared to premixed human insulins and found no difference in lowering fasting glucose, reducing HbA1c levels, rates of hypoglycemia, or weight gain and found only decreased postprandial glucose levels with premixed insulin analogs.[78] A meta-analysis has found that premixed degludec/aspart, a long-acting basal analog with rapid-acting insulin, is associated with a reduction of fasting glucose levels compared to human premixed insulin, with no difference in HbA1c levels or rates of hypoglycemia.[79]

►**Table 1** includes a summary of the most recent systematic reviews comparing insulin analogs and human insulins.

## Cost Considerations

For patients who use insulin, the medication forms a significant part of their health budget. The limited availability and unaffordability of insulin constitutes a big challenge in low-income countries and is a major cause for higher rates of uncontrolled glucose leading to acute and chronic complications of diabetes.[80–83] As an example, in the United States, the cost of insulin was estimated at $6,000 annually per person and accounted for about 20% of the direct medical costs of diabetes in 2018.[84] The prices of insulin have increased significantly over the past two decades. In the United States and just from 2005 to 2011, the cost increase was 114% for regular insulin and NPH insulin, 116% for insulin glargine, 117% for insulin aspart, and 134% for insulin lispro.[84] For the period from 2002 and 2013, there was an increase in the cost of all insulin preparations by more than 300%, while the cost of insulin analogs was higher than human insulins by more than 200%.[85] In the United Kingdom and between 2000 and 2009, the overall spending on insulin doubled which was attributed to the major shift from human insulins to insulin analogs as the use of insulin analogs increased enormously from 12 to 85%.[86]

The high cost of insulin leading to missing or underuse of insulin is becoming an important barrier to proper patient care not only in low-income and middle-income countries but also in high-income countries. One study has shown that about 25% of patients who were prescribed insulin reported its underuse due to cost issues.[87] A survey conducted by the American Diabetes Association on the use of insulin raised

**Table 1** Recent systematic reviews comparing insulin analogs and human insulins

| Reference | Population | Comparators | Study details | Outcomes |
|---|---|---|---|---|
| Melo et al. (2019)[44] | Children and adults with type 1 diabetes | Rapid-acting insulins analogs and regular insulin | 22 trails<br>Total participants: 6,235<br>Duration: 4 to 64 wk | - Better glucose control (HbA1c and postprandial glucose) with rapid-acting insulins<br>- Less total, nocturnal and severe hypoglycemia with rapid-acting insulins |
| Hemmingsen et al. (2021)[23] | Adults with type 1 diabetes | Long-acting insulins (glargine, detemir) with NPH insulin | 18 trials<br>Total participants: 7,412<br>Duration: 24 to 104 wk | - No difference in glucose control (HbA1c levels)<br>- Less severe hypoglycemia with insulin detemir (inconsistent finding)<br>- No difference in health-related quality of life |
| Tricco et al. (2021)[24] | Adults with type 1 diabetes | Long-acting insulins (glargine and detemir) with NPH insulin | 25 studies<br>Total participants: 8,327<br>Duration: 1 to 104 wk | - Better glucose control (HbA1c levels, fasting glucose) with long acting insulins<br>- Less major, serious and nocturnal hypoglycemia<br>- Less weight gain with long-acting insulins |
| Veroniki et al. (2022)[25] | Adults with type 1 diabetes | Long-acting insulins (glargine and detemir) with NPH insulin | 27 trials<br>Total participants: 7,394 patients<br>Duration: 4 to 104 wk | - Better glucose control with long-acting insulins<br>- Less severe hypoglycemia with long-acting insulins |
| Fullerton et al. (2018)[43] | Adults with type 2 diabetes | Rapid-acting insulin analogs with regular insulin | 10 trials<br>Total participants: 2,751<br>Duration: 24 to 104 wk | - No difference in glucose control (HbA1c levels)<br>- No difference in hypoglycemia |
| Semlitsch et al. (2020)[62] | Adults with type 2 diabetes | Long-acting insulins (glargine and detemir) with NPH insulin | 24 trials: 16 trials compared insulin glargine to NPH and 8 trials compared insulin detemir to NPH insulin<br>Total participants: 4,740<br>Duration: 24 wk to 5 y | - No difference in glucose control (HbA1c levels)<br>- Less hypoglycemia with long-acting insulins<br>- No difference in weight gain |

concerns as it revealed that the increase in insulin costs had negatively affected patient care. Because of the high cost of insulin, patients asked their physicians to change their insulin to less expensive types or brands, had to involuntarily take less doses than advised, and, very worryingly, had to miss insulin altogether. Furthermore, a significant percentage of patients had to make the choice between purchasing insulin or paying for other vital requirements such as other health amenities, home utilities, or transportation.[88]

Since the cost of insulin analogs is considerably higher than that of human insulin, several authorities have evaluated the cost-effectiveness of insulin analogs in comparison to human insulins. It was suggested that insulin analogs are worth the high cost by enhancing patients' satisfaction and adherence to therapy, improving quality of life, and possibility of reducing rates of diabetes complications.[89] This led to the evaluation of cost-effectiveness of insulin analog therapy in comparison to human insulins. These studies were based on models that analyzed the projected advantages of insulin analogs such as flexibility, convenience, satisfaction, improvement in HbA1c levels, the expected lowering of diabetes complications, and decreased costs for hypoglycemia including visits to the emergency department and hospitalization, and decreased fear of hypoglycemia. Many of these studies were based on computer models and projected costs based on the assumed decreased incidence of long-term diabetes complications and improved quality-adjusted life expectancy. However, the mean difference in HbA1c levels between insulin analogs and human insulins was 0.01 to 0.23%,[84] a change that is likely not clinically significant.[90] This was supported by findings from a cohort study that included 127,600 patients with type 2 diabetes and found no difference in major cardiovascular events, cardiovascular mortality, and overall mortality when insulin analogs were compared to human insulins.[91] A systematic review found that insulin analogs were cost-effective in patients with type 1 diabetes but not for those with type 2 diabetes.[92] A cost-effectiveness analysis demonstrated that cost-effectiveness was only shown in patients with type 1 diabetes who used rapid-acting insulin analogs and concluded that the routine use of insulin analogs, particularly long-acting basal analogs in type 2 diabetes, is unlikely to be associated with efficient use of health care resources.[93] A cohort study that included 14,635 patients with type 2 diabetes found that switching insulin analogs to human insulins resulted in a minimal increase in HbA1c levels (by 0.14%), no difference in serious hypoglycemic or hyperglycemic episodes and a significant cost savings to the health care system.[94] Despite the borderline advantage of basal insulin analogs over NPH insulin, the lack of clinical evidence of rapid-acting insulins over regular insulin for patients with type 2 diabetes and the substantial higher cost, the use of insulin analogs has been steadily increasing compared to human insulins over the last decades leading to the dominance of insulin analogs particularly in developed and high-income countries.[84,95,96] Heavy promotion of insulin analogs by the pharmaceutical industry is an important contributing factor.[97] The different types of insulin analogs and human insulins along with their costs are listed in ►Table 2.

## Professional Guidelines

Given the presumed advantages and cost difference between insulin analogs and human insulins, several professional organizations have issued recommendations on the proper

**Table 2** Types of insulins and the cost of 1,000 units[a]

| Insulin type | Insulin product | Dosage form[b] Cost | |
|---|---|---|---|
| Human insulins Short-acting | Regular | 10 mL vial | $3.0 |
| Intermediate-acting | NPH | 10 mL vial | $3.0 |
| Premixed | NPH/Regular 70/30 | 10 mL vial | $3.0 |
| Insulin analogs Rapid-acting | Lispro Lispro Aspart Aspart Fast-acting Aspart[c] Glulisine[c] | 10 mL vial 3 mL pen 10 mL vial 3 mL pen 3 mL pen 3 mL pen | $17.9 $36.5 $15.6 $22.9 $42.5 $34.5 |
| Long-acting | Glargine U-100 Glargine U-100 Glargine U-300 Detemir Degludec U-100 | 10 mL vial 3 mL pen 1.5 mL pen 3 mL pen 3 mL pen | $37.5 $31.7 $50.0 $39.8 $55.6 |
| Premixed | Lispro 75/25 Lispro 50/50[c] Aspart 70/30 Degludec/Aspart 70/30[c] | 3 mL pen 3 mL pen 3 mL pen 3 ml pen | $21.4 $38.5 $24.3 $80.9 |

Abbreviation: NPH, neutral protamine Hagedorn.
[a]Cost at Hamad Medical Corporation pharmacy, Qatar.
[b]10 mL vial contains 1,000 units of insulin; 3 mL pen contains 300 units of insulin.
[c]Items not available at the Hamad Medical Corporation; prices from outside pharmacy.

selection of insulin for patients with diabetes. The American Diabetes Association recommends the use of rapid-acting insulin analogs and suggests the use of long-acting insulin analogs over NPH to reduce the risk of hypoglycemia for patients with type 1 diabetes. For patients with type 2 diabetes, the association notes that the advantages of long-acting analogs over NPH are modest and may not persist and highlights the importance of cost consideration while it emphasizes that there are no differences between rapid-acting insulin analogs and human insulin.[71]

The Canadian Agency for Drugs and Technologies in Health recommends that NPH insulin be considered as first-line therapy in both type 1 and 2 diabetes and acknowledges that although the evidence is limited and inconsistent, long-acting insulin analogs can be used for patients who experience significant hypoglycemia with NPH. For bolus insulin therapy, the agency recommends either regular human insulin or rapid-acting insulin analogs for patients with type 1 diabetes except adolescent patients for whom rapid-acting insulin analogs are recommended. For patients with type 2 diabetes requiring meal insulin, the agency recommends that regular human insulin be considered first and rapid-acting insulin analogs reserved for those who experience significant hypoglycemia while taking human insulin with acknowledgment that the evidence is limited and inconsistent.[98]

The National Institute for Health and Care Excellence in the United Kingdom recommends the use of insulin detemir for patients with type 1 diabetes and to use insulin glargine or degludec if detemir is not tolerated, in the presence of nocturnal hypoglycemia or in case of patient's preference.[99] Rapid-acting insulin is recommended for patients with type 1 diabetes. For patients with type 2 diabetes, the institute recommends NPH insulin as the first option and to use insulin detemir or glargine if there is recurrent symptomatic hypoglycemia or for those using NPH twice daily. Regular insulin is recommended as an initial option and rapid-acting insulin is to be used in case of hypoglycemia, patient's preference, or high postprandial glucose levels.[100]

The World Health Organization issued recommendations on the use of insulin for patients with type 1 diabetes and type 2 diabetes in low-resource settings that are directed to both low- and high-income countries.[101] The organization assigned a strong recommendation for the use of human insulins (regular and NPH insulins) for patients with type 1 diabetes and those with type 2 diabetes for whom insulin is prescribed and assigned a weak recommendation for the use of long-acting insulin analogs for adults with type 1 or type 2 diabetes who develop recurrent severe hypoglycemia while on human insulins. ►Table 3 includes a summary of professional guidelines on the use of human and analog insulins in patients with type 1 diabetes as well as those with type 2 diabetes.

## Conclusion

Patient's profile, including the type of diabetes, risks and occurrence of hypoglycemia, and expense of insulin therapy

**Table 3** Professional guidelines on the use of human and analog insulins in adults

| Organization | Type 1 diabetes | Type 2 diabetes |
|---|---|---|
| American Diabetes Association[71] | - The use of long-acting insulin analogs is suggested to reduce the risk of hypoglycemia<br>- The use of rapid-acting insulin analogs is recommended | - The advantages of long-acting analogs over NPH are modest and may not persist<br>- Cost should be considered when selecting between long-acting insulin and NPH<br>- There are no differences between rapid-acting insulin analogs and human insulin |
| The Canadian Agency for Drugs and Technologies in Health[98] | - NPH insulin to be considered as first-line therapy<br>- Long-acting insulin analogs can be used for patients who experience significant hypoglycemia with NPH<br>- Either regular insulin or rapid-acting insulin analogs can be used except adolescent patients for whom rapid-acting insulin analogs are recommended | - NPH insulin to be considered as first-line therapy<br>- Long-acting insulin analogs can be used for patients who experience significant hypoglycemia with NPH<br>- Regular insulin to be considered first and rapid-acting insulin analogues reserved for those who experienced significant hypoglycemia while taking regular insulin |
| National Institute for Health and Care Excellence (United Kingdom)[99,100] | - Insulin detemir is recommended<br>- Use insulin glargine or degludec if detemir is not tolerated, in the presence of nocturnal hypoglycemia or in case of patient's preference<br>- Rapid-acting insulin is recommended | - NPH insulin is recommended<br>- Use insulin detemir or glargine if there is recurrent symptomatic hypoglycemia or for those using NPH twice daily<br>- Regular insulin is recommended<br>- Rapid-acting insulins in cases of hypoglycemia, patient's preference or high postprandial glucose levels |
| World Health Organization[101] | - NPH as first choice<br>- Long-acting insulin analogs for those who developed recurrent severe hypoglycemia while on human insulins<br>- Regular insulin as first choice | - NPH as first choice<br>- Long-acting insulin analogs for those who developed recurrent severe hypoglycemia while on human insulins<br>- Regular insulin as first choice |

Abbreviation: NPH, neutral protamine Hagedorn.

should be considered when clinicians decide between insulin analogs and human insulins. For patients with type 1 diabetes, rapid-acting insulin analogs are preferred over regular human insulins given the associated benefits of better glucose control, decreased risk of hypoglycemia, and cost-effectiveness. Long-acting basal insulins may be considered in patients with type 1 diabetes with attention to the cost and are recommended for patients who develop significant hypoglycemia while on NPH insulin. For patients with type 2 diabetes who require insulin, NPH insulin is still a reasonable option, particularly when cost is an important factor; long-acting basal analogs can be considered in patients who develop significant hypoglycemia-particularly nocturnal, while on NPH insulin. Rapid-acting insulin analogs offer no obvious clinical advantages over regular human insulin in patients with type 2 diabetes except convenience and considerable attention to the cost difference compared to human insulin should be contemplated before implementing their routine use. Similarly, premixed insulin analogs have not shown clear advantages over premixed human insulins and their routine use cannot be justified.

### Compliance with Ethical Principles
No ethical approval is required.

### Authors' Contributions
M.S.E. was responsible for drafting of the article. M.E. and M.I.D. were responsible for critical revision. M.S.E. and M.I.D. were responsible for final approval.

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